

Docket No.: 284112US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF: :
ATSUSHI YAMAGISHI, et al. : EXAMINER: SUTTON, D.C.
SERIAL NO.: 10/564,368 :
FILED: JANUARY 12, 2006 : ART UNIT: 1612
FOR: ORAL ACTIVITY COMPOSITION

DECLARATION UNDER 37 C.F.R. § 1.132

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

Sir:

Now comes Mr. Atsushi Yamagishi who deposes and states that:

1. I am a graduate of the Graduate School of Nagaoka University of Technology, Materials Science and Technology, and received my Master's degree in the field of Materials Science and Technology, in the year 1988.
2. I have been employed by Kao Corporation, for 21 years involved in research and development of hair care products from 1988 to 1999 and then involved in research and development of oral products from 1999 to present.
3. I understand the English language or, at least, that the contents of the Declaration were made clear to me prior to executing the same.
4. The following experiments were carried out by me or under my direct supervision and control.

5. The following experimental procedure was followed:

Two-part compositions (one claimed product and three comparative examples) were prepared as shown in Table 1 below. Part A and Part B of each composition were diluted with artificial saliva as shown in Table 2A and 2B to 3 fold and used in the following procedure.

A HAP pellet was immersed alternately in Part A solution and Part B solution (for 10 seconds for each solution). This treatment was repeated 3 cycles. For Comparative example B1, a HAP pellet was also immersed once in a mixture of Part A and Part B for 3 minutes.

Table 1

		(wt %)			
		Comp. Ex. B1 (US5,858,333 Example 5)	Comp. Ex. B2	Example (Claimed product)	Comp. Ex. B3
A	Calcium nitrate	3.8	3.8	-	-
	Calcium glycerophosphate	-	-	3.42	3.42
	Glycerine	25	25	25	25
	MFP ^{*1)}	-	1.89	1.89	1.89
	Purified water	74	balance	balance	balance
		pH 5.6	pH 5.5	pH 8.1	pH 8.1
B	Potassium phosphate (anhydrous)	4	4	4	4
	Sodium fluoride	0.55	0.55	0.55	-
	Glycerine	25	25	25	25
	Purified water	balance	balance	balance	balance
	Acetate	q.s.	q.s.	q.s.	q.s.
		pH 5.5	pH 5.5	pH about 4	pH about 4
pH in a mixture		5.5	5.5	5.5	5.5
fluorine uptake 1 ($\mu\text{g}/\text{cm}^2$) ^{*2)}		0.75	0.82	2.00	0.05
fluorine uptake 2 ($\mu\text{g}/\text{cm}^2$) ^{*3)}		1.2	-	-	-

*1) The molar amount of MFP was comparative to that of 0.55wt% of sodium fluoride

*2) 3 times immersion

*3) 3 minutes immersion just after preparing the mixture of Part A and Part B

Table 2A: Components of artificial saliva

	mM	g/L
CaCl ₂	1.5	0.1665
KH ₂ PO ₄	5	0.6805
NaCl	5	0.2925
KCl	20	1.49
NaHCO ₃	3	0.252

pH 7.0

Table 2B: Ionic concentration in artificial saliva

Ion species	Total (mM)
Ca	1.5
PO ₄	5
Na	8
K	25
Cl	29.5
HCO ₃	3

6. The experiment and tables above appeared in my Declaration under 37 C.F.R. §1.132 executed on February 20, 2009. Table 1 has been updated to include the pH of individual compositions (A) and (B). Comparative Examples B1 and B2 differ from Example (Claimed product) in the pH of individual compositions (A) and (B), since the compositions of Comparative Examples B1 and B2 are consistent with and representative of US 5,858,333 ("Winston").

7. The following results were obtained

As shown in Table 1 above, the amount of fluorine uptake derived from the claimed product was nearly three times larger ($2.00 \mu\text{g}/\text{cm}^2$ vs. $0.75 \mu\text{g}/\text{cm}^2$) than that derived from Comparative Example B1 (Example 5 composition of Winston). Comparing with the Comparative Example B2, which is the Example 5 composition of Winston further containing MFP in Part A, the claimed product resulted in more than two-fold fluorine uptake ($2.00 \mu\text{g}/\text{cm}^2$ vs. $0.82 \mu\text{g}/\text{cm}^2$). In Comparative Example B3, in which MFP was contained in Part A as the only fluorine supplier, fluorine uptake was poor ($0.05 (2.00 \mu\text{g}/\text{cm}^2$ vs. $0.75 \mu\text{g}/\text{cm}^2)$).

8. The foregoing comparative experiment compared the claimed product to Example 5 of Winston, which, of the Examples, provides the highest increase in hardness (see Table

VII) and believed the best comparative example to the claimed product. Example 3 of Winston could not be replicated for this comparison because the Example 3 composition was difficult to mix and prepare well due to the low water content in Part B.

9. Winston disclose that the cationic part (i.e., Part A) may contain MFP (monofluorophosphate) with calcium salt, but it is less desirable due to the potential loss of fluoride (see, column 9, lines 17-21). As a result, Winston does not provide any Examples in which MFP is used. Thus, based on the disclosure of Winston, the artisan would have expected that the presence of MFP in the cationic part (i.e., Part A) would result in the loss of fluoride and would be dissuaded from using MFP in this part. Indeed, as illustrated in Comparative Example B2 above, adding MFP to part A of Example 5 of Winston resulted in poor fluorine uptake.

In contrast to the expectation presented by the disclosure of Winston, the claimed product, which includes MFP with calcium salt (i.e., in Part A), leads to excellent fluoride uptake rather than resulting in loss of fluoride (see, Table 1 above). Such excellent fluoride uptake (i.e., two-fold over Winston's composition with MFP in Part A and nearly three-fold of Winston's exemplified composition) provided by the claimed invention is in no way expected from the disclosure of Winston.

This result is also unexpected even when considering the disclosures of US 4,048,300 (Tomlinson), US 4,083,955 (Grabenstetter), US 5,605,675 (Usen et al), and/or US 6,287,120 (Wiesel).

10. To further illustrate the unexpected nature of the present invention when considering the disclosures of US 4,048,300 (Tomlinson), US 4,083,955 (Grabenstetter), US

6,287,120 (Wiesel), and/or US 5,605,675 (Usen et al), the following additional experiments were performed.

11. The following experimental procedure was followed:

Two-part compositions (one claimed product and three comparative examples) were prepared as shown in Table 3 below. Part A and Part B of each composition were diluted with artificial saliva as shown in Table 2A and 2B to 3 fold and used in the following procedure.

A HAP pellet was immersed alternately in Part A solution and Part B solution (for 10 seconds for each solution). This treatment was repeated 3 cycles. For Comparative example C1, a HAP pellet was also immersed once in a mixture of Part A and Part B for 3 minutes.

For this experiment the pH of the individual compositions were adjusted by using NaOH as a pH regulator of the cationic composition to have a pH the same as the Examples of the specification.

Table 3 (wt %)

		Comp. Ex. C1	Comp. Ex. C2	Example (Claimed product)	Comp. Ex. C3
A	Calcium nitrate	3.8	3.8	-	-
	Calcium glycerophosphate	-	-	3.42	3.42
	Glycerine	25	25	25	25
	MFP ^{*1)}	-	1.89	1.89	1.89
	Purified water	balance	balance	balance	balance
	Sodium hydrate	q.s.	q.s.	-	-
	Total	100	100	100	100
	pH	8.12 ^{*2)}	8.02	8.12	8.1
B	Potassium phosphate (anhydrous)	4	4	4	4
	Sodium fluoride	0.55	0.55	0.55	-
	Glycerine	25	25	25	25
	Purified water	balance	balance	balance	balance
	Acetate	q.s.	q.s.	q.s.	q.s.
	Total	100	100	100	100
	pH	4.12	4.28	4.07	4.1
	pH after mixing an equal amount of each composition A and B	3.1	4.00	5.50	5.50

*1) The molar amount of MFP was comparative to that of 0.55wt% of sodium fluoride

*2) Composition A of Comparative Example C1 lowered its pH as soon as left in the atmosphere since its buffering capacity of pH of about 8 is weak.

* Each solution is employed by triple-diluting with artificial saliva.

12. The results set forth in Table 4 were obtained for the experiment set forth in the preceding paragraph and Table 3:

Table 4

Fluorine uptake ($\mu\text{g}/\text{cm}^2$)	Comp. Ex. C1	Comp. Ex. C2	Example (Claimed product)	Comp. Ex. C3
Alternative treatment with each solution each three times	8.25	6.21	2.00	0.05
Treatment with mixed solution for three minutes	0.87	0.31	---	0.01
HAP surface	melted (and damaged)	melted (and damaged)	produced thin layer	no change
Salt of calcium phosphate	produced	produced	unproduced	unproduced

* After alternative treatment, HAP pellet surface of each sample was observed and it was confirmed whether a salt of calcium phosphate was produced.

** In Comparative Examples C1 and C2, damages of HAP pellets were observed.

*** In Comparative Examples C1 and C2, calcium fluoride was observed to be produced, but a salt of calcium phosphate was not.

13. The experiment performed in paragraphs 11 and 12, above, each pH of Composition A and B was adjusted to be same as those of examples in the claimed invention. The pH values of each mixed solution were shown in Table 3 since pH values would have an effect on a production of a salt of calcium phosphate.

The experiment result thereof appearing in Table 4 show that fluorine uptake amount of Comparative Examples C1 and C2 could be increased since each pH thereof was very low. However, it was also clearly shown that HAP pellets were apparently melted because of their low pH. Thus, the effect of monofluorophosphate could not be compared since a salt of calcium phosphate was not produced.

14. Since the HAP pellets were melted in the experiment above, we investigated the buffering capacity of the mixed solution of Compositions A and B. In this experiment a solution containing calcium nitrate, calcium lactate or calcium glycerophosphate was added

to an acidic solution of sodium fluoride containing phosphate (pH 3.7) and each pH was measured. The fluorine concentration and phosphate concentration of the latter solution is respectively 0.5 and 0.15 mol/l and the calcium concentration of the former solution 0.1 mol/l.

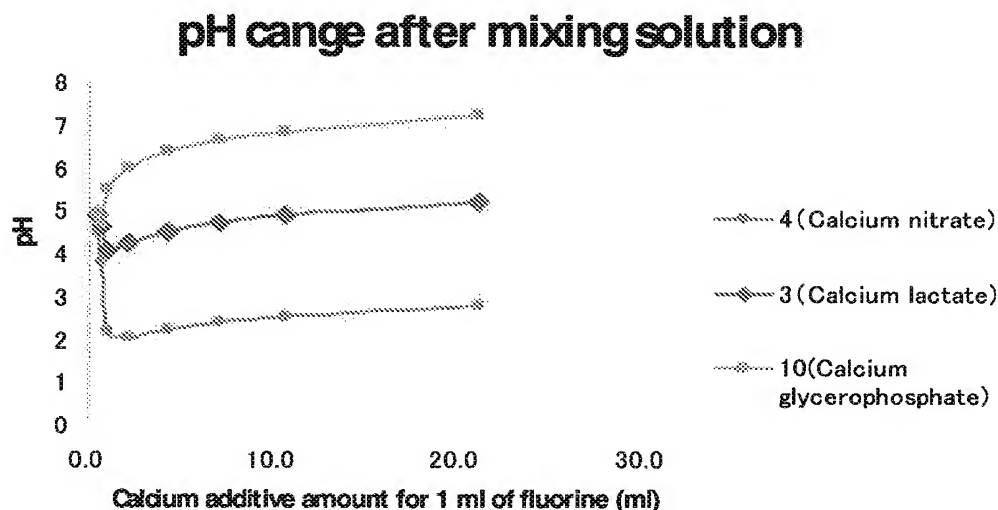
15. The results obtained are illustrated in Table 5

Table 5

Calcium amount for 1ml of fluorine (ml)	pH value		
	4 (Calcium nitrate)	3 (Calcium lactate)	10 (Calcium glycerophosphate)
21.1	2.75	5.2	7.2
10.5	2.49	4.89	6.83
7.0	2.36	4.71	6.62
4.2	2.2	4.5	6.36
2.1	2.04	4.21	5.97
1.1	2.14	4.03	5.48
0.7	3.8	4.62	4.71
0.4	4.47	4.88	4.92

16. Since most of fluorine is present as hydrogen fluoride (HF) and therefore a large number of protons are emitted into the solution by producing calcium fluoride (CaF_2), the mixed solution containing calcium nitrate rapidly lowers its pH because calcium nitrate having 1 or less of pKa has no buffering action. Calcium lactate has its buffering capacity near 4 to 5 of pH and calcium phosphate has its buffering capacity near neutrality. Accordingly, their pH would change as shown in Fig. 1:

Fig. 1



17. In accordance with the foregoing experimental results, the mixed solution has low pH in Comparative Examples C1 and C2 because its buffering capacity of calcium salts included therein and therefore teeth would not be repaired, but melted. In addition, Comparative Examples C1 and C2 do not show the effect of the claimed invention, which effects are to increase production of a salt of calcium phosphate and to increase fluorine uptake.

This result is also unexpected even when considering the disclosures of US 4,048,300 (Tomlinson), US 4,083,955 (Grabenstetter), US 5,605,675 (Usen et al), and/or US 6,287,120 (Wiesel).

18. US 4,048,300 (Tomlinson) disclose alternative treatment with each composition. US 4,048,300 (Tomlinson) makes no reference to calcium glycerophosphate. Indeed, in the Example 12 of US 4,048,300 (Tomlinson) calcium nitrate is used. When calcium nitrate was

used for the substitution of calcium glycerophosphate, the surface of HAP was melted. These results are shown in Table 3 and 4 above (see Comparative Examples C1 and C2).

To explain in detail, reference is made to the following Figures 2-1, 2-2, 2-3.

Fig. 2-1

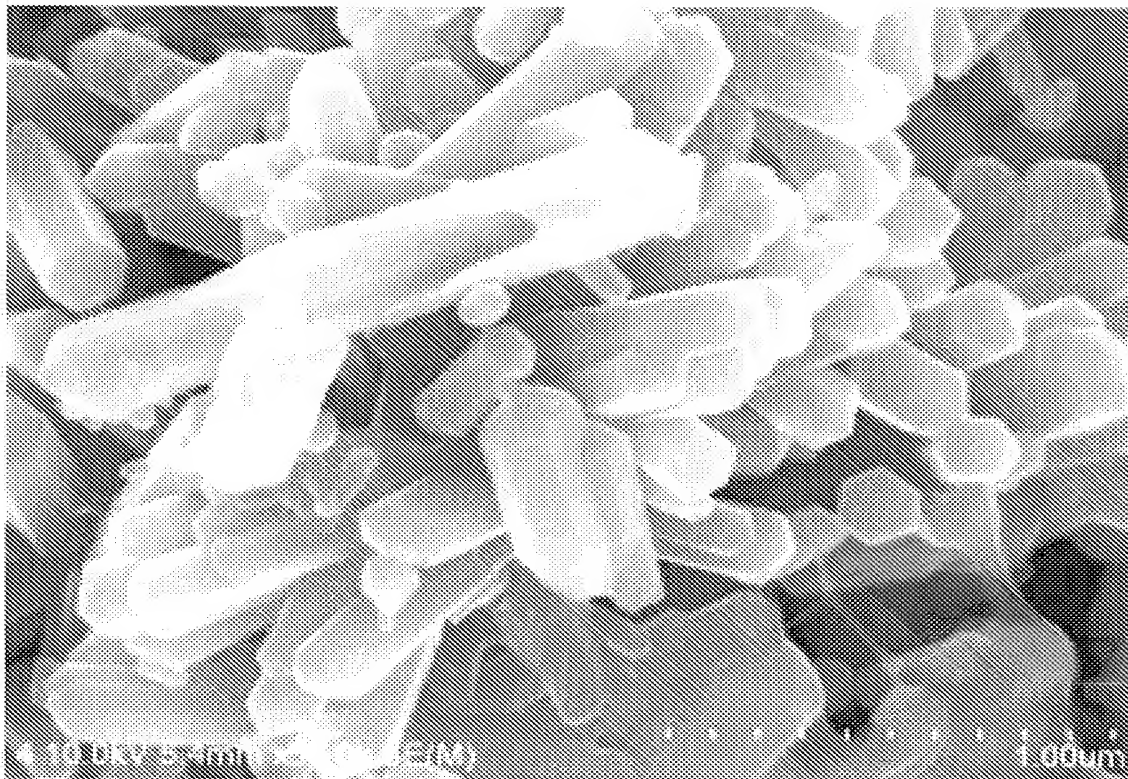


Fig. 2-1 shows HAP powder before treatment. Columnar crystals of HAP are observed.

Fig. 2-2

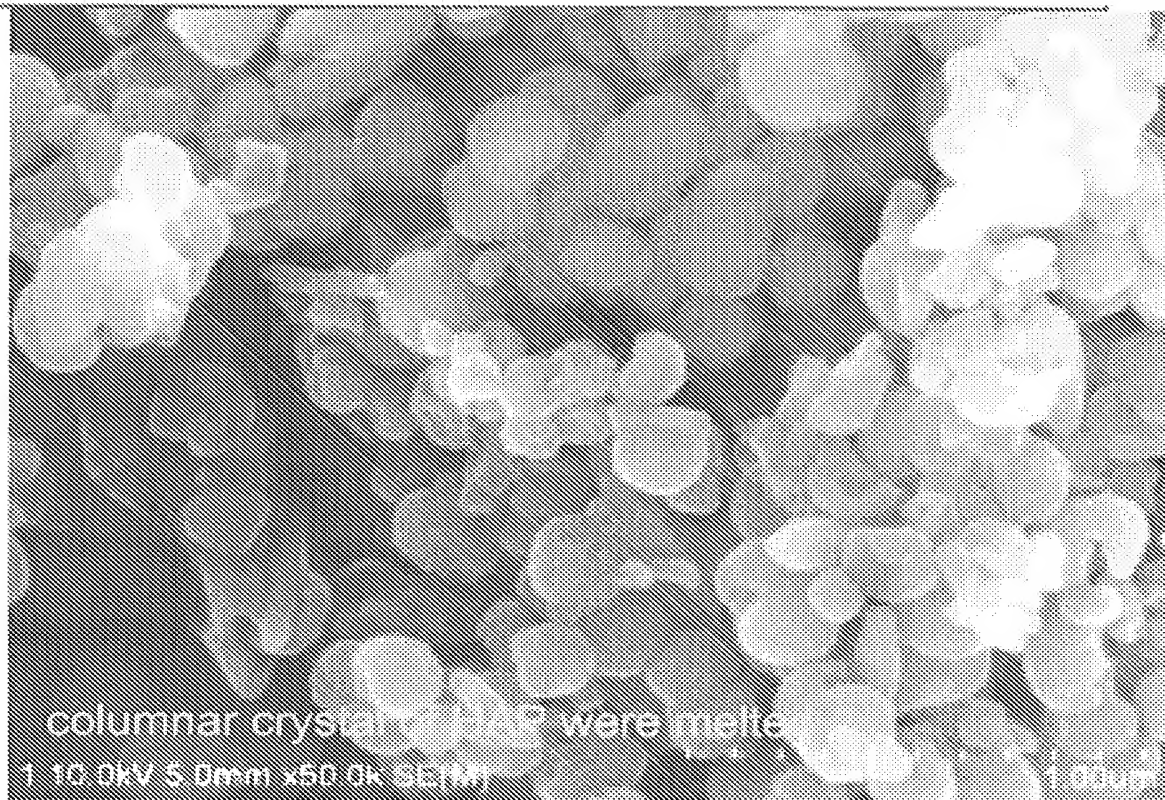


Fig. 2-2 shows HAP powder after treatment by the composition identified as Comparative Example C1 in Table 3 above. Columnar crystals of HAP are melted. This result shows that HAP is melted when Comparative Example C1 is applied by alternative treatment. In Table 4 above, fluoride uptake of Comparative Examples C1 and C2 are 8.25 and 6.21, respectively. These values look higher than the example of the claimed invention at first glance. However, this does not tell the complete story as HAP was melted and the calcium ion is released from HAP. The calcium ion is combined with fluoride and becomes calcium fluoride on the surface of HAP. Calcium fluoride is easily dissolved in saliva and, as a result, calcium fluoride in the saliva was detected for fluoride uptake.

Fig. 2-3



Fig. 2-3 shows HAP powder after treatment by the composition identified as Example in Table 3 above. It is observed that columnar crystal of HAP was not melted and many small crystals were attached on the surface of HAP. These small crystals contain “calcium fluoride”, “hydroxyapatite”, and “calcium phosphate”. When calcium fluoride coexists with hydroxyapatite and/or calcium phosphate, calcium fluoride is hardly dissolved into saliva and fluoride is taken into HAP. The fluoride taken into HAP forms into FHAP ($\text{Ca}_{10}(\text{PO}_4)_6\text{F}_2$).

As a reminder Comparative Examples C1 and C2 contain calcium nitrate and Example contains calcium glycerophosphate. The foregoing evidence when taken together with the data in Table 4 clearly show the criticality in using calcium glycerophosphate, which would not be apparent from the disclosures of US 4,048,300 (Tomlinson), US 4,083,955 (Grabenstetter), US 5,605,675 (Usen et al), and/or US 6,287,120 (Wiesel) or even US 5,858,333 (“Winston”).

19. The following Tables 6 and 7 provide the solubility and concentration in saliva:

Table 6

	Solubility
Calcium fluoride	18 mg/l
Hydroxyapatite	1 to 3 mg/l
Calcium hydrogen phosphate	200 mg/l

Table 7

	concentration in saliva
Calcium	20 to 30 mg/l
Fluoride	0.03 mg/l
Phosphate	200 to 300 mg/l

Since the concentration of fluoride in saliva is low, calcium fluoride is easily dissolved into saliva. In contrast, because concentration of phosphate in saliva is high, calcium hydrogen phosphate is hardly dissolved into saliva. Therefore, calcium fluoride must coexist with hydroxyapatite and/or calcium phosphate for re-calcification (re-mineralization).

Figures 3-1 and 3-2 provide an illustration of the scheme to provide a better understanding.

Fig. 3-1 Comp. Ex. (calcium nitrate)

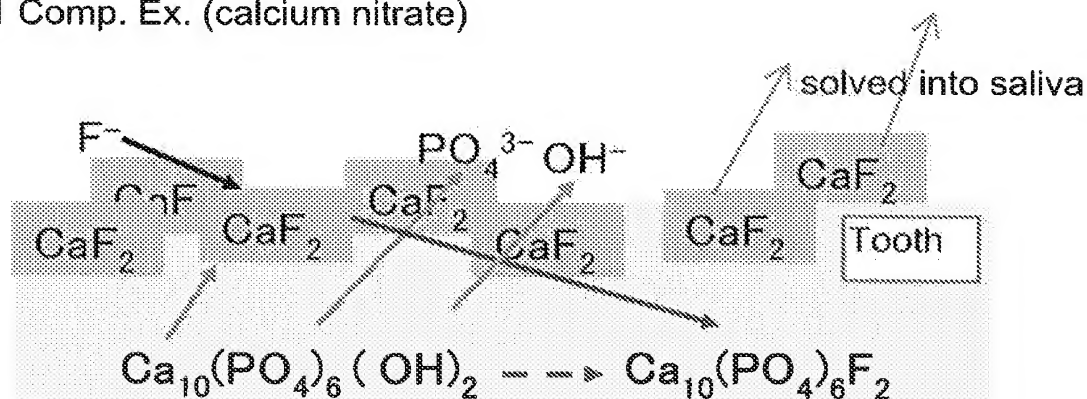
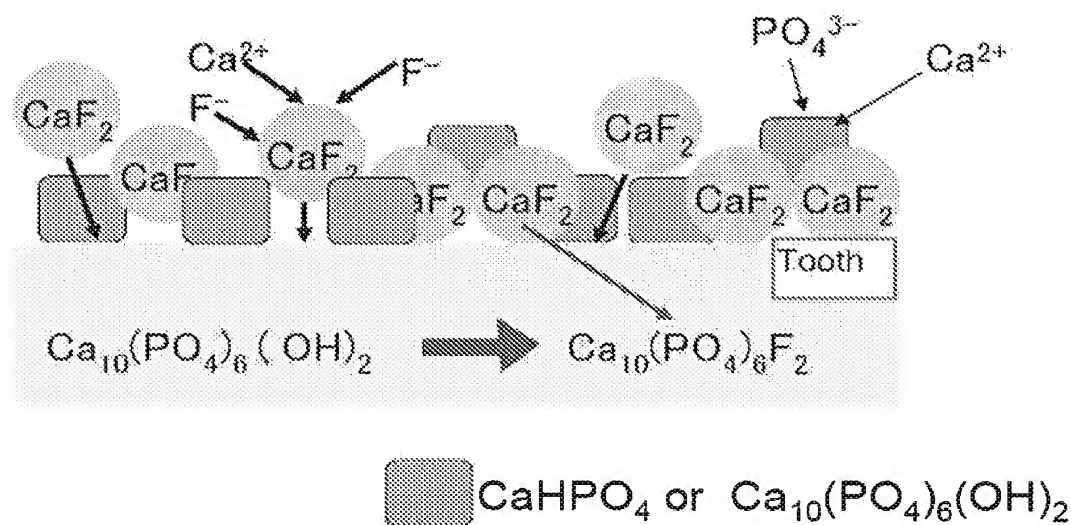


Fig. 3-2 Examples. (calcium glycerophosphate)



20. In the alternative treatment with two compositions as claimed, an unexpected result was obtained when the composition contains a calcium polyol phosphate (such as calcium glycerophosphate). Since US 4,048,300 (Tomlinson) does not disclose calcium polyol phosphate and US 5,858,333 (Winston) as well as US 5,605,675 (Usen et al) do not disclose alternative treatment, claimed method is not obvious. Moreover, the claimed invention provides an unexpected result when considering the additional disclosures of US 4,083,955 (Grabenstetter) and US 6,287,120 (Wiesel).

21. I declare further that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

22. Further Declarant saith not

Atsushi Yamagishi
Name: Atsushi Yamagishi

October 1, 2010
Date